REMARKS

Claims 1, 3-14, 16, 17, 22, 26, 29, 31, 35, 38-40, 44, 45, 47, 49, 50-54, 57-59, 61-65, 67, 68, and 70-91 are pending. Claims 2, 5-7, 15, 18-21 , 23-25, 27, 28, 30, 32 – 34 , 36, 37, 41-43 , 46, 49, 55, 56, 60, 66, and 69 are canceled. Claims 4, 16, 17, 22, 26, 29, 31, 35, 38, 40, 44, 45, 47, 48, 50-54, 57-59, 61-65, 67, 68 and 70 are withdrawn from consideration. Claims 92 and 93 are added. Applicants note that the Examiner has not indicated the status of claims 75-91. However, Applicants believe that these claims were intended to be listed as withdrawn given that they depend, directly or indirectly, from claims that are withdrawn. Accordingly, upon entry of the present amendment, claims 1, 3-14, 16, 17, 22, 26, 29, 31, 35, 38-40, 44, 45, 47, 49, 50-54, 57-59, 61-65, 67, 68, and 70-93 will be pending.

Support for the Amendment

Support for the amendments is found in the specification and claims as originally filed. For example, support for new claims 92 and 93, is found at page 27, lines 1-6, at page 30, lines 23-26, and Figure 2. No new matter is added.

Objections to the Specification

The objection to the specification for including embedded hyperlinks is overcome by the present amendment.

Objections to the Claims

The objection to the claim 1 as containing a grammatical error is overcome by the present amendment.

The Examiner objects to claim 1 for failing to include the term "D33S1169." Applicants note that the term "D33S1169" does not appear in Applicants' specification. Applicants believe the Examiner is referring to D22S1169, which term is now recited, thereby obviating the rejection.

Double Patenting

Claims 1, 3-7 and 71 are provisionally rejected over claims 50-54 and 61-63 of USSN. 11/793,575. Applicants respectfully traverse the rejection. Applicants will address the obviousness-type double patenting rejection upon a finding that the claims (that will be pending upon entry of the amendments presented herein) are in condition for allowance, but for the instant double patenting rejection.

Rejections under 35 U.S.C. § 112, second paragraph

Claim 71 is rejected under 35 U.S.C. § 112, second paragraph, for allegedly lacking clarity. The Examiner asserts that the phrase "between microsatellite loci D22S929 and D22S1169" is unclear, and the metes and bounds of the claimed subject matter cannot be determined. Applicants respectfully disagree. The position of microsatellite markers on the human genome was publically available at the time the present application was filed, as evidenced in Ingvarsson et al., Breast Cancer Res. 4:1-6, 2002 (page 2, left column, first full paragraph; of record). Therefore, the positions of D22S929 and D22S1169 would be readily apparent to one of skill in the art. Withdrawal of the rejection under 35 U.S.C. § 112, second paragraph is respectfully requested.

Rejections under 35 U.S.C. § 112, first paragraph

Written Description

Claims 1, 3-13, and 71-75 are directed to methods of determining a predisposition or resistance to infection by obtaining a DNA bearing sample from a subject, and assaying the sample to identify the alleles present at microsatellite loci D22S929, D22S277, D22S264, D22S423 & D22S418, D22S272 or D22S1169. Claims 1, 3-13, and 71-75 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking an adequate written description. In support of the rejection, the Examiner asserts that Applicants have failed to describe a sufficient number of species to support the claimed genus. More specifically, the Examiner asserts that the genus of nucleic

acid species is defined by function, i.e., resistance to infection. For the reasons detailed below, Applicants respectfully disagree with the rejection and request that it be withdrawn.

An adequate written description of the invention may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the invention had possession of the claimed invention (M.P.E.P. 2163.04 II.A.3(a)). Applicants' specification clearly describes methods of determining a predisposition or resistance to infection by obtaining a DNA bearing sample from a subject, and assaying the sample to identify the alleles present at microsatellite loci. Applicants identified 42 individuals that were resistant to HIV infection despite repeated exposure to the virus (page 25, first full paragraph under the header "EUI and HIV-1-infected individuals"). Applicants found that the genotypes of these individuals identified a number of simple single length polymorphisms associated with the presence of mucosal anti-HIV IgA in HIV-1-uninfected individuals (page 30, lines 23-26). At the D22S423 loci the correlation of uninfected individuals having allele 221 was significantly higher than in HIV-1 infected individuals (page 30, lines 26-28). At loci D22S277 alleles 156 and 159 there was also a statistically significant difference in the frequency with which these alleles were observed in the uninfected group relative to HIV-1 infected individuals (page 31, lines 14-15). These results provide strong evidence that genotypes at this segment of chromosome 22 are associated with enhanced immune responses to HIV-1 in uninfected individuals (page 32, lines 12-16).

In view of this important discovery, Applicants have clearly defined the segment of chromosome 22 that is associated with a predisposition or resistance to infection in terms of microsatellite loci D22S929, D22S277, D22S264, D22S423 & D22S418, D22S272 or D22S1169 as recited in claim 1. The sequence of a DNA sample obtained from a subject could be readily assayed to identify the alleles present at these microsatellite loci, just as described in Applicants' specification at page 30, lines 23-26, where Applicants assayed the genotypes of 42 human subjects to determine the method of determine that the presence of particular alleles was indicative of a

resistance to infection. One skilled in the art provided with Applicant's specification would clearly recognize that Applicant was in possession of the claimed invention as of the filing date. Nothing more is required. Accordingly, the written description rejection should also be withdrawn.

Enablement

Claims 1, 3-13, and 71-75 are further rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. Although the Examiner acknowledges that Applicants have enabled methods for determining resistance to HIV infection associated with the claimed microsatellite markers, the Examiner alleges that Applicants have failed to demonstrate that such methods could be used to detect resistance to any other infection. Applicants respectfully disagree and traverse the rejection. However, without in any way acquiescing to the rejection and in order to expedite prosecution of the application, the claims have been amended as set forth above, thereby obviating the enablement rejection.

Rejections under 35 U.S.C. § 103

Claims 1, 3-12, and 71-74 are rejected as allegedly obvious over Stephens et al., Am. J. Hum. Genet. 62:1507-1515, 1998 (hereinafter "Stephens"), Super et al., J. Virol. 73:7848-7852, 1999, Sheehy, Nature 418:646-650, 1999, and Jarmuz et al., Genom. 79:285-296, 2002. Claims 13 and 75 are further rejected as allegedly obvious over the aforementioned references and Ingvarsson et al., Breast Cancer Res. 4:1-6, 2002 (hereinafter "Ingvarsson"). In support of the obviousness rejection, the Examiner states:

> It would be obvious to modify the methods of Stephens to include more microsatellite loci from human chromosome 22, as suggested by Super et al., containing retrovirus-resistant genes like the HIV-inhibiting APOBEC3 as suggested by Sheehy and Jarmuz.

As detailed below, Applicants respectfully disagree with the rejection and request that it be withdrawn.

Applicants were the first to discover that genotypes at the segment of chromosome 22 defined by microsatellite loci D22S929, D22S277, D22S264, D22S423 & D22S418, D22S272 or D22S1169 were associated with resistance to HIV infection. This discovery was made by characterizing alleles present in individuals that were not infected with HIV despite repeated exposure to the virus (page 25, first full paragraph under the header "EUI and HIV-1-infected individuals"). Surprisingly, Applicants found that the genotypes of these individuals identified a number of simple single length polymorphisms associated with the presence of mucosal anti-HIV IgA in HIV-1-uninfected individuals (page 30, lines 23-26). None of the art cited by the Examiner recognized that the particular microsatellite loci of chromosome 22 identified by Applicants are associated with enhanced immune responses to HIV-1 in uninfected individuals (page 32, lines 12-16).

In particular, the prior art fails to describe any genotype that confers resistance to HIV infection. Applicants were the first to establish two phenotypes that are unrelated to APOBEC3 that confer a defense against infection by HIV and by studying the syntenic region in mice where death from infection occurs faster. The multiple-exposed seronegative patients described by Applicants are not infected with HIV despite repeated exposures. This distinguishes them from long-term non-progressive patients who are infected with HIV, but who do not develop full-blown AIDS. None of the prior art cited by the Examiner, alone or in any combination, ties alleles at the segment of chromosome 22 defined by microsatellite loci D22S929, D22S277, D22S264, D22S423 & D22S418, D22S272 or D22S1169 to resistance to HIV virus infection

In order to make out a prima facie showing of obviousness, the Office Action must provide some motivation to combine the references, the combination of references must teach or suggest each and every element of the claimed invention, and there must be some reasonable expectation of success in making and using the invention as claimed. (MPEP §2141). In the present case, the references cited in the Office Action

fail to teach or suggest all of the claim limitations; fail to provide the requisite motivation to combine; and fail to provide a reasonable expectation of success.

Stephens describes haplotype analysis for a 32 base pair deletion in the CCR5 gene that mediates chemokine responsiveness. Individuals homozygous for this mutation are resistant to HIV infection in the sense that although infected with HIV, their disease fails to progress. These patients are readily distinguishable from the subjects described by Applicants who are resistant to HIV infection. More importantly, Stephens fails to teach or suggest that alleles present on chromosome 22 at the particular microsatellite loci recited in claim 1 are associated with resistance to HIV virus infection. To remedy the deficiencies of Stephens, the Examiner cites Sheehy.

Sheehy describes the isolation of a gene that inhibits HIV-1 infection in non-permissive cells. This gene is expressed in human cells that are resistant to HIV infection (i.e., non-permissive cells), but is inactive in human T cells, which are the principal cell target for HIV infection. Sheehy found that the non-permissive cells express an anti-viral protein termed CEM15. The gene encoding CEM15 is present on chromosome 22. Sheehy fails to teach or suggest that mutations on chromosome 22 would confer resistance to HIV infection. In fact, Sheehy's discovery that a gene present on chromosome 22 confers resistance to HIV infection in non-permissive cells would suggest that alterations in the *CEM15* gene or in a *CEM15* regulatory sequence would reduce or eliminate the HIV-resistance conferred by *CEM15*. Thus, Sheehy teaches away from the notion that sequence changes on chromosome 22 would be associated with HIV resistance. Therefore, Sheehy cannot be used to remedy the deficiencies of Stephens.

Like Sheehy, Jarmuz fails to teach or suggest that mutations on chromosome 22 are associated with HIV resistance. Jarmuz merely describes the tissue-specific expression of APOBEC1 family members (Abstract). Jarmuz teaches that certain of these family members are present on chromosome 22 (Abstract). Jarmuz fails to define the role of APOBEC3 with regard to HIV infection. There is nothing in Jarmuz that

remedies the deficiencies of Stephens and Sheehy. To remedy the deficiencies of Jarmuz, Stephens, and Sheehy, the Examiner cites Super.

Super describes the mapping of Rfv3 on mouse chromosome 15 (Abstract). Rfv3 provides resistance to the Friend virus (page 7848, left column, first paragraph). Super fails to address human immunity to HIV, much less suggest that alleles on chromosome 22 would be associated with HIV resistance. Thus, Super fails to remedy the deficiencies of the other cited references.

In sum, none of the aforementioned references, alone or in any combination, teaches or suggests that alleles at the segment of chromosome 22 defined by microsatellite loci D22S929, D22S277, D22S264, D22S423 & D22S418, D22S272 or D22S1169 are associated with enhanced immune responses to HIV-1. Furthermore, none of these references teaches or suggests that the haplotype analysis described by Stephens should be used to identify HIV-resistant alleles present at the aforementioned microsatellite markers. Therefore, the obviousness rejection over Stephens, Sheehy, Super, and Jarmuz should be withdrawn.

The Examiner rejects claims 13 and 75, which are directed to methods of determining a predisposition or resistance to infection by obtaining a DNA bearing sample from a subject, and assaying the sample using single strand length polymorphism (SSLP) analysis with specific flanking primer sets for PCR amplification of specific microsatellite markers, over Sheehy, Super, Jarmuz and Ingvarsson. As detailed above, Stephens, Sheehy, Super, and Jarmuz fail to teach or suggest assaying for HIV-resistant alleles present at the recited microsatellite markers. Ingvarsson fails to remedy these deficiencies. Ingvarsson merely describes a mutation analysis of the CHK2 gene in breast carcinoma using certain overlapping microsatellite loci. Like Sheehy, Super, and Jarmuz, Ingvarsson fails to teach or suggest that HIV-resistant alleles may be present at the aforementioned microsatellite markers. Accordingly, withdrawal of the rejection over Ingvarsson on this basis is requested.

Furthermore, Applicants submit that Ingvarsson is not analagous art and cannot be used to support a rejection under 35 U.S.C. § 103(a); (M.P.E.P. 2141.01(a)). To determine whether a reference is from an analogous art, a two-fold analysis is required:

> First, we decide if the reference is within the field of the inventor's endeavor. If it is not, we proceed to determine whether the reference is reasonably pertinent to the particular problem with which the inventor was involved. *In re Wood*, 599 F.2d 1032, 1036 (C.C.P.A. 1979)

The Wood court first considers whether the reference is within the inventor's field and then considers whether the reference is pertinent to the problem the inventor is trying to solve.

Ingvarsson is not within the field of Applicant's invention. Ingvarsson relates to a mutational analysis of the CHK2 gene in breast cancer (Abstract). In contrast, Applicant's invention relates to resistance to HIV virus infection. Resistance to infection with a sexually transmitted virus is distinct and distinguishable from the field of breast cancer. Thus, Ingvarsson fails the first prong of the test set forth by the court in Wood.

Furthermore, Ingvarsson is also not reasonably pertinent to the problem that Applicants were involved in solving. Applicants were interested characterizing alleles associated with HIV infection resistance. The mutations described by Ingvarsson are associated with tumor growth (Abstract), and are not pertinent to Applicants work on HIV infection. Thus, Ingvarsson fails the second prong of the test established by the court in In re Wood.

In sum, because Ingvarsson is outside of the field of viral infections and is not reasonably pertinent to the problem of HIV viral resistance that Applicants were involved in solving, Ingvarsson is clearly nonanalagous art, and therefore cannot be used to support the obviousness rejection (M.P.E.P. 2141.01(a)). Accordingly, the rejection of the claims over Ingvarsson should be withdrawn.

CONCLUSION

In view of the above amendment, Applicants believe the pending application is in condition for allowance.

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Respectfully submitted,

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